Integrating Immunohistochemistry for Biomarker Detection in NSCLC: A Step Toward Precision Therapy

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Background

Advances in NSCLC treatment increasingly depend on biomarker-driven precision strategies, with targeted therapies offering clear advantages over cytotoxic agents. However, the rapid expansion of actionable biomarkers—many of them rare—makes their routine detection and integration into clinical practice challenging. Accurate and efficient biomarker characterization is therefore essential to ensure timely and appropriate therapy selection for each patient.

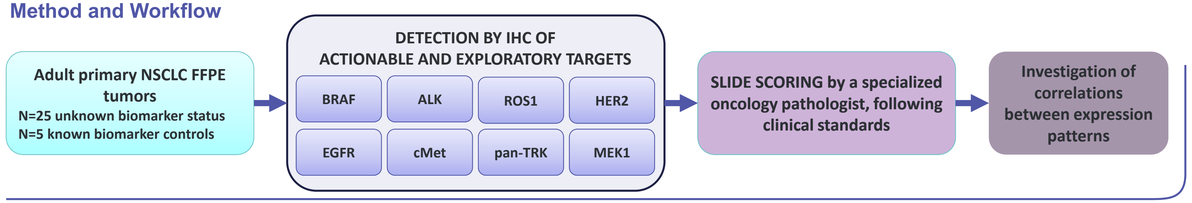
Introduction

Lung cancer causes over 1.8 million deaths annually, with non-small cell lung cancer (NSCLC) representing about 85% of cases[1,2]. Because NSCLC is highly genetically diverse, comprehensive biomarker testing—using tools such as next-generation sequencing (NGS) panels and immunohistochemistry (IHC)—is essential to guide optimal treatment. International guidelines (CAP, IASLC, AMP, ASCO, NCCN[3], and the Canadian consensus) help define which biomarkers and assays should be used.

Target	Selected Rx*	Antibody Clone	Expected Positivity Rate
ALK	Crizotinib, Ceritinib, Alectinib, Brigatinib, Lorlatinib	D5F3	3%[4-5]
ROS1 (+/- FISH)	Crizotinib, Lorlatinib, Entrectinib	SP364	1-2%[4-6]
HER2	Trastuzumab, Pertuzumab	DG44	1-5%
EGFR	Erlotinib, Gefitinib, Dacomitinib, Osimertinib	3C6	10-15%[4-5]
Pan-TRK	Larotrectinib, Entrectinib	EPR17341	<1%[6]
BRAF	Vemurafenib, Dabrafenib	VE1	4%[4-5]
cMet	Crizotinib, Tivantinib, Onartuzumab	SP44	3-4%[7]
MEK1	Trametinib, Binimetinib, Selumetinib	H-8	/

Table 1. Druggable and exploratory targets with pre-identified antibodies to be tested through simplex IHC on NSCLC formalin-fixed, paraffin-embedded (FFPE). *Selected treatments that target the specific biomarker.

Method and Workflow



Results: IHC data concordance study with genetic profiling and observed prevalence

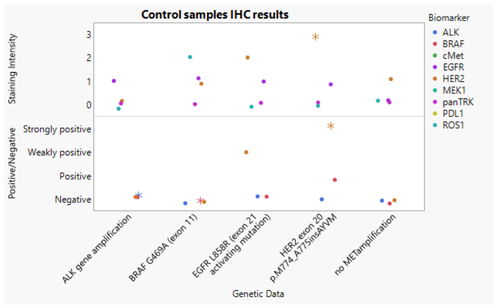


Fig 1. IHC staining results for tissue controls

** Indicates slides for which pathologist made a comment*

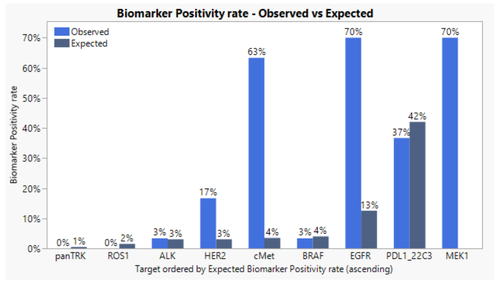


Fig 2. Biomarkers positivity rates in tested samples

IHC performance on control samples (Figure 1) showed strong concordance with NGS for HER2, cMET, and EGFR, confirming the reliability of the IHC panel for these targets. HER2 expression was notably intense compared with other controls. BRAF showed no IHC staining, consistent with a non-V600E mutation and supporting assay specificity despite an atypical pattern (weak cytoplasmic/moderate nuclear signal) noted by the pathologist. For ALK, gene amplification detected by NGS did not translate into strong protein expression; however, focal IHC positivity prompted recommendation for reflex fluorescence in situ hybridization.(FISH)/NGS, underscoring the role of IHC as a relevant screening step for ALK alterations. In the set of 25 unknown samples, biomarker positivity rates (Figure 2) aligned with published NSCLC prevalence. ALK, BRAF, and PD-L1 frequencies fell within expected ranges, while EGFR and cMet appeared slightly higher, further supporting the utility of IHC for rapid upfront stratification before molecular testing. No positive cases were identified for ROS1, or pan-TRK, consistent with their low occurrence in NSCLC. Together, these data highlight IHC as a robust first-line approach for detecting principal NSCLC biomarkers and guiding efficient reflex FISH/NGS testing.

Results: Evaluating biomarkers relationships

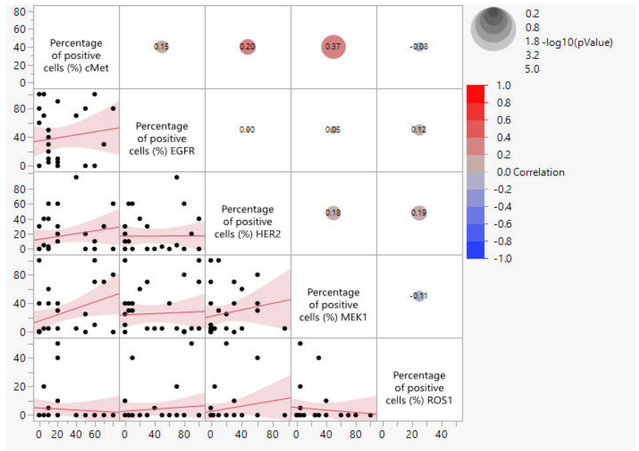


Fig 3. Scatter plot Matrix showing correlation of IHC percentage of positive cells between tested biomarkers. panTRK results were omitted as no sample showed positivity for this marker.

In the 30 NSCLC samples from Cerba Research Biobank, IHC revealed heterogeneous biomarker expression across the cohort. Pan-TRK, BRAF, ALK and ROS1 showed very low staining, preventing reliable interpretation. Although some samples reached up to 50% focal staining, none met criteria for true positivity, as no diffuse 2+/3+ ROS1-like patterns were observed by the international pathologist. The graph illustrates both the distribution of detectable biomarkers and the low prevalence of rare targets and demonstrates how IHC-based biomarker matrices can support more accurate treatment assignment for patients.

Results: Samples's biomarkers signature

The scatter plot matrix revealed noticeable patterns of co-occurrence among the tested biomarkers. The strongest association was observed between cMet and MEK1, with 37% of samples showing concurrent expression, suggesting a potential linkage in signaling pathways or shared regulatory mechanisms. A similarly prominent trend was seen between cMet and HER2, which co-occurred in 20% of cases, indicating that these alterations may cluster within a subset of NSCLC tumors. These relationships highlight the ability of IHC-based profiling to uncover biomarker patterns that may inform both diagnostic interpretation and subsequent molecular testing strategies.

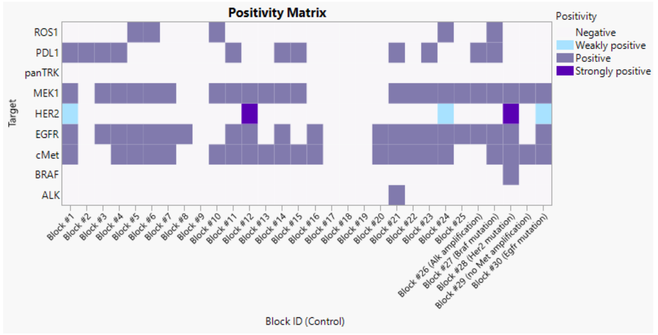


Fig 4. Positivity matrix showing biomarker positivity for each tested sample

Conclusion

Across control and unknown NSCLC samples, IHC demonstrated strong reliability for detecting key biomarkers and showed high concordance with NGS for HER2, cMet, and EGFR. The panel effectively identified expected positivity rates in the 25-sample cohort, with ALK, BRAF, and PD-L1 aligning with known prevalence and EGFR/MEK1 appearing slightly higher, supporting IHC as a rapid first-line screening method before reflex molecular testing. Rare targets such as BRAF, ROS1, ALK and pan-TRK showed minimal or non-interpretable staining, consistent with their low occurrence in NSCLC. Visualization tools—including scatter plot matrices and heat maps—highlighted heterogeneous biomarker expression and revealed notable co-occurrence patterns, particularly between cMet with MEK1 and HER2. Together, these findings demonstrate that IHC provides a robust, efficient approach for initial NSCLC biomarker stratification, supports identification of clinically relevant expression patterns, and helps guide timely and appropriate downstream testing and treatment selection. **Together, these findings support the role of IHC as a robust and accessible screening method for most actionable biomarkers, particularly in settings without routine NGS. Its integration into pathology workflows can help optimize patient selection for precision medicine and clinical trial enrollment.**

1. About lung cancer. American Cancer Society;
2. World Health Organization (WHO). Lung Cancer Fact Sheet. June 26, 2023;
3. National Comprehensive Cancer Network (NCCN) 2025;
4. American Lung Association;
5. American Cancer Association;
6. Facchinetti et al. Can Treat Rev;2017;55;83-95;
7. Cancer Support Community.

Disclosures: M G-D, RB, JS & AF are Cerba Research employees or past employees. RG is a consultant. Study is sponsored by Cerba Research